



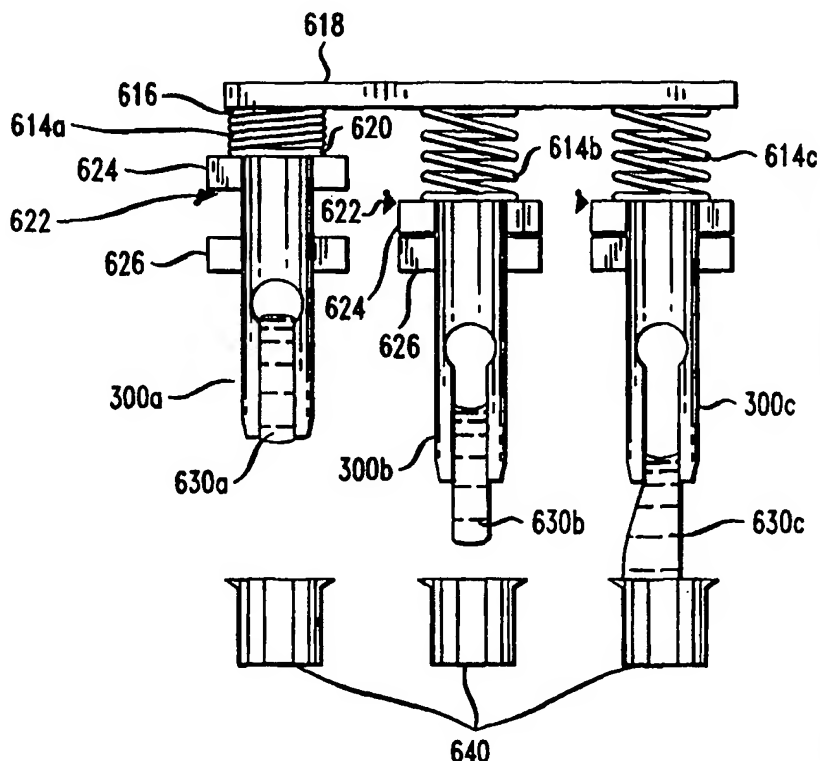
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(21) International Application Number: PCT/US98/26826 (22) International Filing Date: 17 December 1998 (17.12.98) (30) Priority Data: 08/993,106 18 December 1997 (18.12.97) US (71) Applicant (for all designated States except US): PHARMA- COPEIA, INC. [US/US]; Box CN 5350, Princeton, NJ 08543 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): FEYGIN, Ilya [-/US]; 853 Mountainside Drive, Mountainside, NJ 07092 (US). (74) Agent: BREYER, Wayne. S.; DeMont & Breyer, LLC, 35 Malus Lane, Middletown, NJ 07748 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.	

(54) Title: ARTICLE FOR DISPENSING SMALL VOLUMES OF LIQUID

(57) Abstract

A method for handling and dispensing small volumes (630a) of liquid, and apparatus for carrying out the method, are disclosed. A small volume of liquid (630a), which is retained within a fluid-dispensing member (300a), is dispensed therefrom by accelerating, and then abruptly decelerating, the member (300a). The abrupt deceleration causes the retained liquid (630a) to discharge. The discharged liquid (630c) may be directed toward a receiver (640). A micro volume liquid dispenser for practicing the method includes a plurality of fluid-dispensing members (300a, 300b, 300c) configured for aspirating and retaining a small volume (630a) via capillary action. The dispenser further includes an actuator (614a, 614b, 614c) for moving/accelerating the fluid-dispensing members (300a, 300b, 300c) and for stopping/abruptly decelerating (626) the fluid-dispensing members.



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ARTICLE FOR DISPENSING SMALL VOLUMES OF LIQUID

Field of the Invention

The present invention relates to an article and method for handling and
5 dispensing small volumes of liquid.

Background of the Invention

During the course of research and development, production and other
technological activities in a variety of different fields, a need arises to handle, transfer
and dispense very small volumes of liquid. "Micro volume" liquid handling and
10 dispensing systems, suitable for handling liquid volumes on the order of microliter,
have been developed to satisfy such a need.

Micro volume liquid dispensing systems are categorizable, generally, into one
of two groups based on the way in which they dispense their charge of liquid. In a
first group of such micro volume delivery systems, a portion of the dispensable liquid,
15 while still in its dispenser, is brought into contact with a receiving body ("the
receiver"). Based on a difference in surface tension between liquid in the dispenser
and liquid contacting the receiver, the liquid is drawn out of the dispenser and into the
receiver. Such systems may be categorized as requiring "touch-off." Exemplary
touch-off-based micro volume dispensing devices include capillary tubes, wettable
20 pegs or pins and syringes using "drop touch-off," among others. Dispensing devices
included within the first group tend to be mechanically simple and inexpensive.
Unfortunately, it may be undesirable or impractical to bring the dispenser close
enough to the receiver to effect liquid contact. In particular, in the medical, chemical
and biological arts, such close contact may cause undesirable carryover or cross
25 contamination wherein a substance in the receiver is drawn into or onto the dispenser.
Moreover, cleaning capillary tubes and syringes, such as may be required between
each touch-off due to a change in the dispensed liquid or to avoid cross
contamination, can be problematic.

In a second group of micro volume liquid dispensing systems, which may be categorized as "non touch-off," the dispensable liquid is forcibly ejected from the dispenser. Exemplary devices utilizing such an ejection method include piezo or thermally-actuated liquid ejectors as are often used in print heads, solenoid modulators of pressurized liquid flows and micrometering pumps. Such devices avoid the aforementioned drawback associated with touch-off; however, they suffer from other drawbacks. In particular, both piezo and thermally actuated liquid ejectors are limited to use with extremely small volumes of liquid, and typically require very clean and specially-developed fluids. Such restrictions limit the utility of liquid ejectors in chemical, biochemical and related arts. Pumps and flow modulators are usually very expensive, bulky, slow, have limited reliability and are often incompatible with biochemical or chemical reagents, as well.

Moreover, most of the conventional micro volume liquid dispensers mentioned above are not readily adaptable for use in systems requiring multiple dispensing ports. As such, their use is precluded or substantially curtailed in high throughput chemistry and screening applications. Thus, there is a need for a simple and reliable system suitable for transferring small volumes of a variety of liquids and possessing multi-point dispensing capability.

Summary of the Invention

A method for handling and dispensing small volumes of liquid, and apparatus for carrying out the method, are disclosed. In accordance with the invention, a small volume of liquid, which is retained within a carrier, is dispensed therefrom by accelerating, and then abruptly decelerating, the carrier. The dispensed liquid is directed toward a receiver.

The method is carried out using a micro volume liquid dispenser that includes, as a liquid carrier, a plurality of fluid-dispensing members. Each fluid-dispensing member comprises two opposed surfaces in spaced relation to one another and suitably configured for aspirating and holding a small volume of liquid via capillary

action. Each fluid-dispensing member retains and delivers a liquid volume within the range of about 0.5 to about 5 microliters. The opposed surfaces are The present micro volume liquid dispenser further includes an actuator for moving/accelerating the fluid-dispensing members and for stopping/abruptly decelerating the fluid-dispensing members. The actuator can use a biasing member, such as a spring, for accelerating the fluid-dispensing members, and a "stop" for abruptly decelerating the fluid-dispensing members. Alternatively, the actuator can utilize more sophisticated pneumatic, hydraulic or electrodynamic systems. As noted above, abruptly decelerating moving fluid-dispensing members causes retained liquid to issue therefrom. Such dispensed liquid can be directed toward, and received by, an intended receiver.

Unlike conventional capillary tubes, the "open" capillary design of the present fluid-dispensing members advantageously allow for efficient cleaning, as is desirable between transfers of different liquids. Moreover, the present micro volume liquid dispenser is a "non touch-off" type of device, avoiding potentially undesirable contact with the receiver. Unlike most conventional non touch-off-based devices, the present dispenser is inexpensive, reliable, fast and compatible with a wide range of biochemical or chemical reagents of varying purity.

Brief Description of the Drawings

Further features of the invention will become more apparent from the following detailed description of specific embodiments thereof when read in conjunction with the accompanying Figures in which:

- FIG. 1 is a flow diagram of a method in accordance with the present invention;
- FIG. 2 shows a first exemplary embodiment of a fluid-dispensing member;
- FIG. 3 shows a second exemplary embodiment of a fluid-dispensing member;
- FIG. 4 shows a third exemplary embodiment of a fluid-dispensing member;
- FIG. 5 shows a conceptual illustration of a micro volume liquid dispenser suitable for carrying out the present method;

FIG. 6 shows a first exemplary embodiment of the micro volume liquid dispenser of FIG. 5;

FIG. 7 shows a second exemplary embodiment of the micro volume liquid dispenser of FIG. 5; and

5 FIG. 8 shows a third exemplary embodiment of the micro volume liquid dispenser of FIG. 5 wherein operation of the dispenser is under microprocessor control.

Detailed Description of the Invention

A method 100 in accordance with the present invention is illustrated by flow diagram in FIG. 1. According to the method, a small volume of liquid is delivered to a receiver by accelerating a liquid-containing carrier, hereinafter referred to as a "fluid-dispensing member," along a first direction, as indicated in operation block 102, and then abruptly decelerating it, as per operation block 104. Abrupt deceleration of the fluid-dispensing member causes liquid retained therein to issue therefrom substantially along the first direction. A receiver is positioned near to the fluid-dispensing member to receive the dispensed liquid.

In a further aspect of the present invention, the present method 100 for liquid delivery is carried out using a micro volume liquid dispenser described in this specification. Such a dispenser incorporates a plurality of the aforementioned fluid-dispensing members, each capable of delivering a liquid volume in the range of about 0.5 to about 5 microliters. Preferably, the liquid carrier is configured to receive and retain its liquid charge via capillary action. A fluid-dispensing member 200 for use in conjunction with the present invention is shown in FIG. 2.

The fluid-dispensing member 200 has two opposed surfaces 202, 204 that are separated by a gap 206. In one embodiment, the surfaces 202 and 204 are concave. Such concave opposed surfaces can be obtained, for example, by forming a slit in a capillary tube. In a second embodiment, the surfaces 202 and 204 are substantially flat. Such flat opposed surfaces can be obtained, for example, forming a slit in a solid

rod. The dimensions of the gap 206 and the surfaces 202, 204 are suitably selected to allow aspiration and retention of a chosen liquid via a capillary effect. It is expected that differences among liquids, e.g., surface tension, will not significantly affect the gap sizing, surface dimensions, etc., of a fluid delivery member 200, such that a
5 single micro volume liquid dispenser according to the invention will be suitable for use with a variety of liquids. A gap 206 having a dimension in the range of about 1 to about 1.5 millimeters (mm), and opposed surfaces 202, 204 having a width of about mm or more are expected to be satisfactory for use with a wide range of liquids.

In some embodiments, such as the exemplary embodiment shown in FIG. 3,
10 the dimension of the gap 206 is adjustable. Such adjustability is provided by a gap adjuster 312. A simple, easily implemented embodiment of such a gap adjuster 312 is a "tightening screw," as is pictured in FIG. 3.

In some embodiments, a discontinuity, disruption or other change in the gap/surfaces is utilized to terminate the capillary action of opposed surfaces 202, 204,
15 thereby allowing a fluid-dispensing member 300 to aspire a predetermined and repeatable volume of liquid. In one exemplary embodiment, shown in FIG. 3, the discontinuity is a "widening" 310 that is located at an inner terminus 308 of the gap 206.

Differences in dimensions between the surfaces 202, 204, or between surface
20 characteristics of the surfaces 202, 204 resulting in local variations in surface tension may cause a deviation in the course of liquid issuing from a fluid-dispensing member. To reduce or eliminate any such deviation for those or other reasons, the fluid-dispensing member includes, in some embodiments, a liquid director 412, such as is shown in FIG. 4. The liquid director 412, configured as a "needle-like" structure in
25 the embodiment shown in FIG. 4, is located within the gap 206 along a centrally-located long axis 1-1 of fluid-dispensing member 400. The liquid director 412 extends beyond opposed surfaces 202, 204 in the aforementioned axial direction.

During the dispensing process, the dispensable volume of liquid slides along the liquid director 412 forming a symmetrical droplet due to its surface tension. The

liquid, after disassociating with the liquid director 412, maintains a substantially straight-line course out of the dispenser along the axis 1-1. It should be understood that liquid directors having other physical configurations, as may be devised by those skilled in the art, and operable to direct a small volume of liquid along a
5 predetermined direction, may suitably be used in place of the aforescribed structure.

The micro volume liquid dispenser further includes an actuator 214 for moving/accelerating the fluid-dispensing members 200, 300 or 400, and for stopping/decelerating the fluid-dispensing members, as shown conceptually in FIG. 5. As described further below, the actuator 214 can utilize any of a number of different
10 types of forces for accelerating and decelerating the fluid-dispensing members. Additionally, different instrumentalities may be used for accelerating and decelerating the fluid-dispensing members, or, alternatively, a single instrumentality can be used for both operations.

An embodiment of a micro volume liquid dispenser 600 according to the
15 present invention is shown in FIG. 6. In the embodiment shown in FIG. 6, the actuator 214 comprises a biasing member configured as a helical spring 614a - 614c, a movable stop member 624 and a fixed stop member 626.

Each helical spring 614a - 614c is attached, at a first end 616, to a rigid base 618, and, at a second end 620, one each to respective fluid-dispensing members 300a -
20 300c. To develop energy for accelerating a fluid-dispensing member, such as the fluid-dispensing member 300a, the spring 614a is placed in a compressive state, as shown in FIG. 6. The spring 614a is maintained in such a compressed state using, for example, a latch 622. To dispense liquid 630a, the latch 622 is released, allowing the spring 614a to expand and release its stored energy. As a result, attached fluid-
25 dispensing member 300a is accelerated in the direction of expansion.

Before an expanding spring, such as the spring 614b, is restored to a fully uncompressed state, movable stop member 624 contacts fixed stop member 626, halting expansion of the spring and abruptly decelerating depending fluid-dispensing member 300b. The abrupt deceleration of a fluid delivery member, such as the fluid-

dispensing members 300b, 300c, causes liquid 630b, 630c retained therein to discharge. The liquid can be discharged into appropriately positioned receivers 640.

It will be appreciated that a wide variety of configurations suitable for accelerating and abruptly decelerating the fluid-dispensing members can be used in conjunction with the present invention. For example, with reference to FIG. 7, rather than attaching a biasing member to each fluid-dispensing member 300a - 300c, the fluid-dispensing members could be attached directly a rigid movable base 718. One or more biasing members, such as helical springs 714a, 714b, each one of which is capable of storing and releasing more energy than any one of the springs 614a - 614c, are placed between the rigid movable base 718 and a second rigid nonmoving surface 720. Latches or the like, not shown, are operable to realizable compress the helical springs 714a, 714b.

In the embodiment shown in FIG. 7, the ability to selectivity discharge a select one or more fluid-dispensing members is forfeited if it is necessary to charge all fluid-dispensing members with liquid at the same time. If such selective discharge is not required, however, the embodiment shown in FIG. 7 offers a simpler configuration than, for example, the embodiment shown in FIG. 6. Of course, by filling only those fluid-dispensing members that are to be discharged in a selected time period, the ability to selectively discharge is retained.

Moreover, as previously noted, it should be understood that a wide variety of forces may be used to accelerate and/or decelerate the fluid-dispensing members 200, 300 and 400. For example, depending upon the surface tension of the dispensable liquid, the force of gravity may impart sufficient acceleration to fluid dispensing members, in an appropriately configured micro volume fluid dispenser according to the present invention, to dislodge the fluid on abrupt deceleration. Further, pneumatic, hydraulic or electrodynamic-based actuators can be used to accelerate and/or decelerate the fluid-dispensing members 200, 300 and 400. Moreover, the operation of the present micro volume liquid dispenser can be automated, such as, for example, by using a microprocessor-based control system, as illustrated in FIG. 8.

In the embodiment illustrated in FIG. 8, the actuator comprises a solenoid 814. A solenoid, the structure and use of which is well known by those skilled in the electrical arts, typically includes a coil, an associated core, and linkage as appropriate to connect to a target device. In the present context, the solenoid is in mechanical communication with a fluid-dispensing member 300(*I*). In the embodiment shown in FIG. 8, a solenoid 814 is provided one for each fluid-dispensing member 300(*I*). Each solenoid 814 is electrically connected to a controllable current source 806 that is operable, in conjunction with other known processing electronics, not shown, to supply a current to a selected solenoid. The controllable current sources 806 is under the control of a microprocessor 810, which is in communication with memory 812 and clock 814.

A dosing schedule is loaded into memory 812. The dosing schedule, which is accessed by the microprocessor 810, provides a time at which some or all of the fluid-dispensing members dispense their charge of liquid. An exemplary dosing schedule might dictate, for example, that fluid-dispensing members 300a - 300c dispense their charge to a first group of segregated regions of a receiver, such as to wells 818a - 818c of microtiter plate 816, at a first time. The schedule might further dictate that fluid-dispensing members 300d - 300f dispense their charge of liquid to wells 818d - 818f of microtiter plate 816 at a second time, and so forth.

At the scheduled time, the microprocessor 810 sends a signal to the controllable current source 808 directing it to apply a current to the solenoids associated with the fluid-dispensing members 300(*i*) scheduled to dispense. The current applied to the solenoid causes a core or rod located near the coil to accelerate rapidly into the coil. A fluid-dispensing member 300(*i*), mechanically linked to the core, is likewise accelerated. Mechanical stops, not shown, are positioned as appropriate to rapidly decelerate the core and the interconnected fluid-dispensing member. Liquid retained in abruptly decelerated fluid-dispensing members is discharged. The process may then be repeated for other fluid-dispensing members scheduled for dispensing at other times.

It will be appreciated that a variety of different control schemes, as will occur to those skilled in the art, can be used to automate operation of the present micro volume liquid dispenser. Moreover, it should be clear that any suitable number of liquid-dispensing members can be included in the present micro volume liquid dispenser. For example, a micro volume liquid dispenser having ninety-six of such liquid dispensers would be advantageous for use with 96-well microtiter plates, such as are in common use in the pharmaceutical industry for conducting biological assays and the like.

Although specific embodiments of this invention have been shown and described herein, it is to be understood that these embodiments are merely illustrative of the many possible specific arrangements that can be devised in application of the principles of the invention. Numerous and varied other arrangements can be devised in accordance with these principles by those of ordinary skill in the art without departing from the scope and spirit of the invention.

I claim:

1. An article for dispensing a small volume of liquid, comprising:
a fluid-dispensing member having two opposed surfaces in spaced relation to one another, the surfaces and space therebetween operable to generate a capillary effect;
5 an actuator operable to accelerate and then abruptly decelerate the fluid-dispensing member, wherein
upon abrupt deceleration, liquid held between the two opposed surfaces is discharged.
- 10 2. The article of claim 1, wherein the fluid-dispensing member has a discontinuity in the spaced opposed surfaces and the space therebetween, said discontinuity operable to terminate the capillary effect.
3. The article of claim 2, wherein the discontinuity is a widening of the space between the opposed surfaces.
- 15 4. The article of claim 1, wherein the fluid-dispensing member further comprises a liquid director physically configured to substantially eliminate deviations in a path followed by liquid discharged from the fluid-dispensing member.
5. The article of claim 4, wherein the physical configuration of the liquid director is substantially needle-like, and wherein the liquid director is disposed within
20 the space between the opposed surfaces and aligned along a centrally-located long axis of the fluid-dispensing member.
6. The article of claim 5, wherein the liquid director extends beyond opposed surfaces of the fluid-dispensing member along the direction of the long axis.

7. The article of claim 1, wherein the opposed surfaces are concave.
8. The article of claim 1, wherein the opposed surfaces are flat.
9. The article of claim 1, wherein the fluid-dispensing member further comprises a gap adjuster operable to change the spacing between the two opposed
5 surfaces.
10. The article of claim 9, wherein the gap adjuster is a tightening screw.
11. The article of claim 1, wherein the actuator comprises a biasing member operable to store energy in a first position, wherein, when released from the
10 first position, a portion of the stored energy is converted to kinetic energy thereby accelerating at least a part of the biasing member and also accelerating the fluid-dispensing member, which is in mechanical communication therewith.
12. The article of claim 1, wherein the actuator further comprises a first and a second stop, wherein the first stop is substantially nonmovable
15 and the second stop is mechanically linked to the fluid-dispensing member and thereby accelerated therewith, and, wherein,
the first stop is suitably positioned to engage the second stop after the second stop has moved a predetermined distance as a result of said acceleration, wherein,
the fluid-dispensing member is abruptly decelerated when the first and second
20 stops engage.
13. The article of claim 1, wherein the first stop is positioned to engage the second stop before substantially all stored energy available for conversion into kinetic energy is so converted.

14. The article of claim 11, wherein the biasing member is a spring.

15. The article of claim 1, further comprising ninety-six fluid-dispensing members, wherein, the ninety-six fluid-dispensing members are arranged so that when liquid in one of the fluid-dispensing members is dispensed, it is receivable by a
5 complementary one of ninety-six wells contained in a suitably-positioned ninety-six well microtiter plate.

16. The article of claim 1, further comprising a microprocessor in communication with a memory and a clock, the microprocessor operable to actuate the actuator according to a dosing schedule.

10 17. The article of claim 16, wherein the microprocessor is in communication with a controllable current source, the controllable current source is in electrical communication with the actuator, and the actuator is a solenoid, wherein,
the microprocessor is operable to send a signal to the controllable current source at a time dictated by the dosing schedule, which controllable current source is
15 operable to apply a current to the solenoid, thereby actuating the solenoid and accelerating the fluid-dispensing member.

18. The article of claim 16, wherein the actuator is configured for pneumatic, hydraulic or electrodynamic operation.

19. A micro volume liquid dispenser, comprising:

a plurality of fluid-dispensing members, each fluid-dispensing member having two opposed surfaces in spaced relation to one another, the surfaces and space therebetween operable to generate a capillary effect;

5 a plurality of biasing elements, mechanically linked, at a first end thereof, one biasing element to one of the fluid-dispensing members, wherein each biasing element is operable to accelerate the mechanically-linked fluid-dispensing member; and

a plurality of first and a second stop members, wherein the plurality of first stop members depend, one from each fluid-dispensing member, so that a depending
10 first stop member is accelerated in conjunction with an associated fluid-dispensing member, and wherein the second stop members are substantially nonmovable and each one is aligned to engage one of the first stop members after it has been accelerated; wherein,

when the first and second stop members engage, the associated fluid-
15 dispensing member is decelerated at a rate sufficient to discharge liquid held between the two opposed surfaces thereof.

20. The micro volume liquid dispenser of claim 19, wherein each fluid-dispensing members has a discontinuity in the spaced opposed surfaces and the space therebetween, said discontinuity operable to terminate the capillary effect.

20 21. The micro volume liquid dispenser of claim 19, wherein each fluid-dispensing member further comprises a liquid director physically configured to substantially eliminate deviations in a path followed by liquid discharged from the fluid dispensing member.

22. A method for discharging a small volume of liquid, comprising the steps of:

accelerating a liquid carrier operable to retain liquid via a capillary effect ; and
abruptly decelerating the liquid carrier, wherein,

5 retained liquid is discharged from the liquid carrier as a result of the abrupt deceleration.

23. The method of claim 22, wherein the step of accelerating further comprises converting the stored energy within a biasing element to kinetic energy that is imparted to the liquid carrier.

24. The method of claim 22, further comprising the step of directing the discharged liquid to a receiver.

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FIG. 1

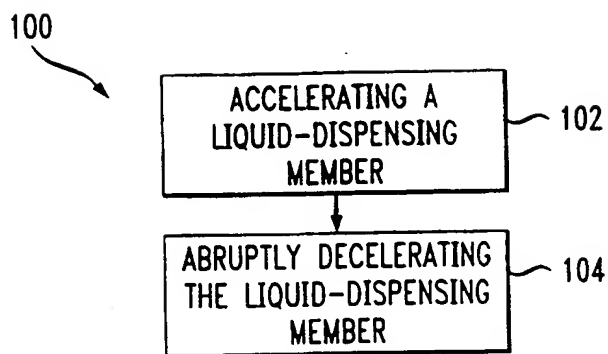


FIG. 2

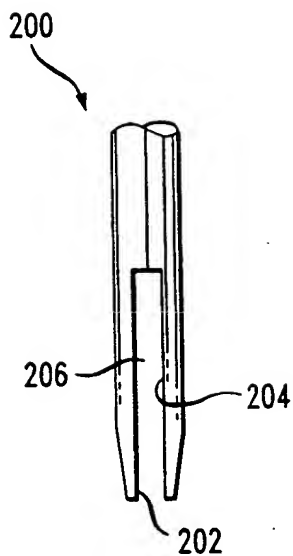


FIG. 3

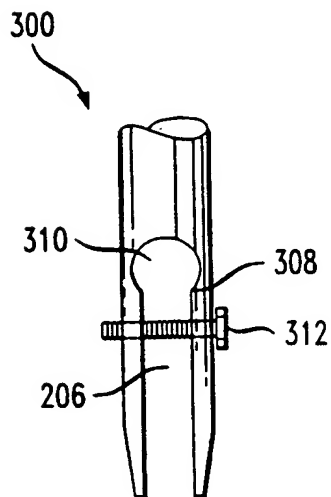
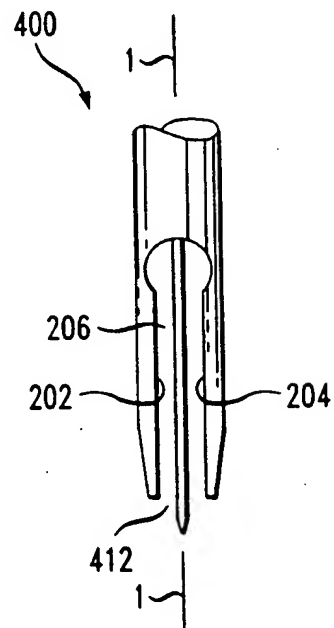


FIG. 4



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FIG. 5

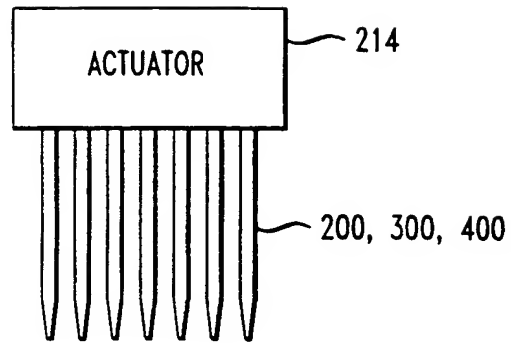
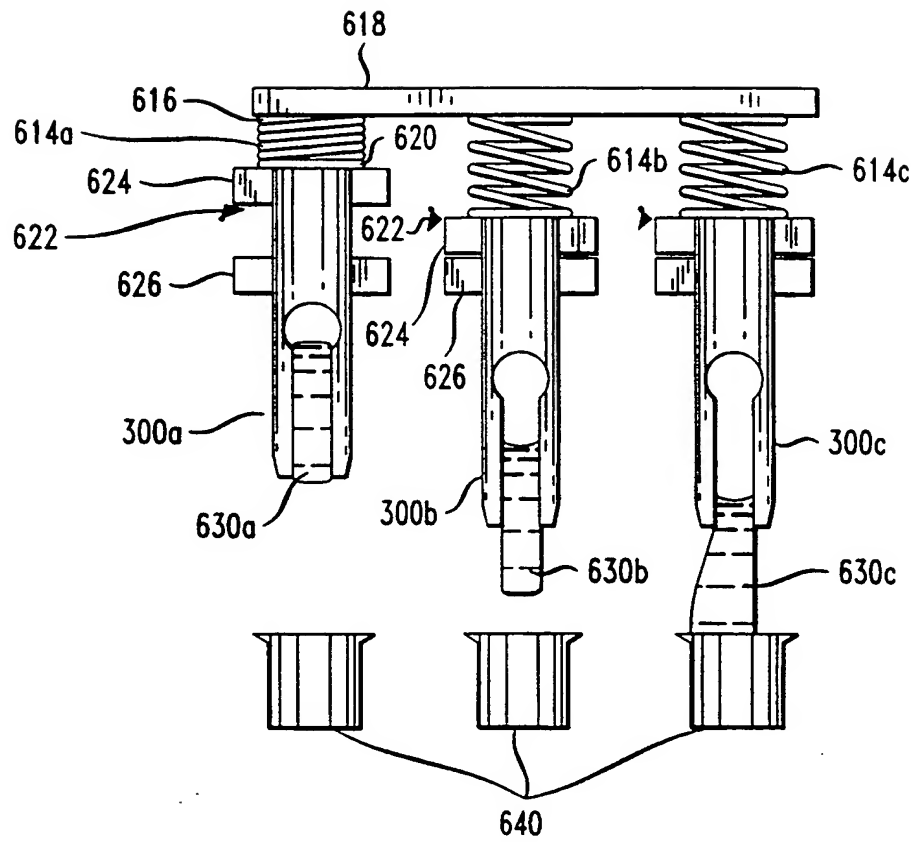


FIG. 6



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FIG. 7

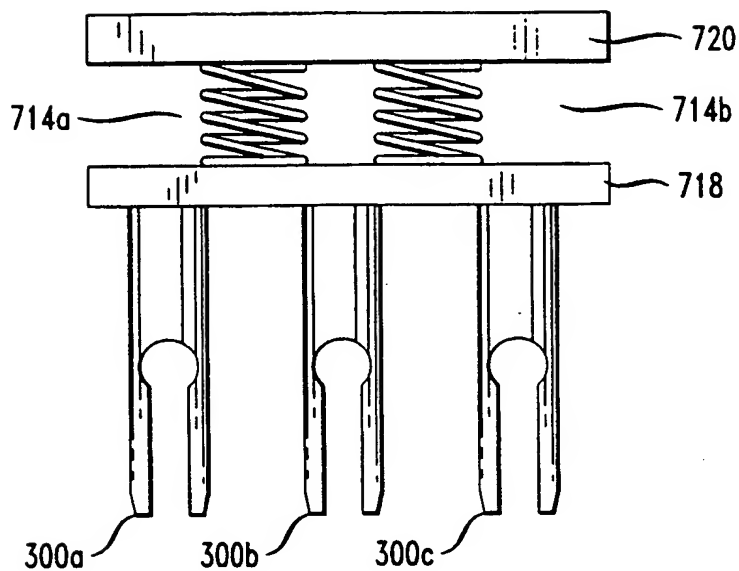
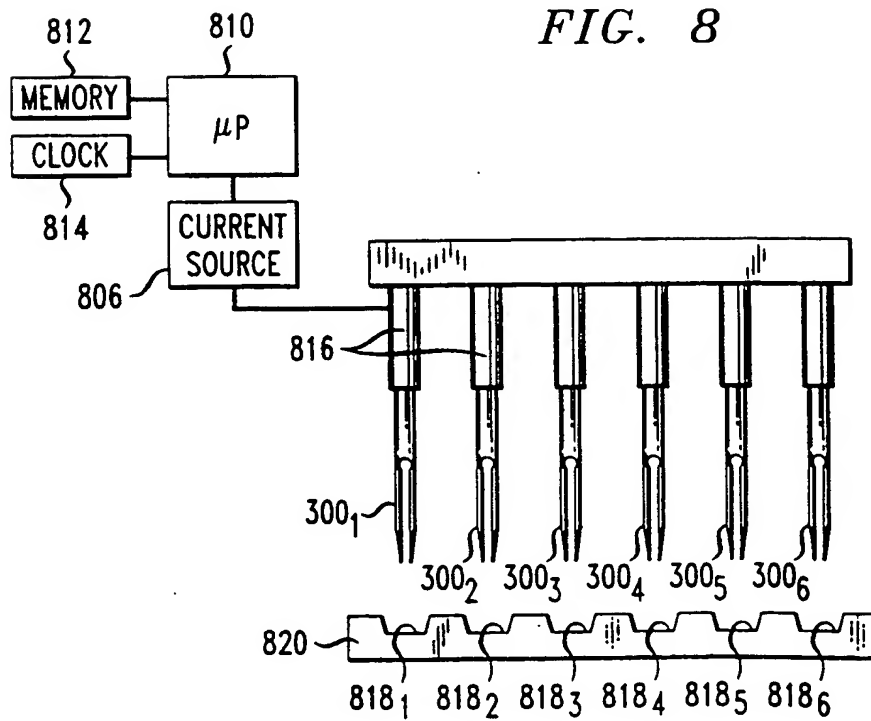


FIG. 8



INTERNAT L SEARCH REPORT

International application No.

PCT/US98/26826

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :G01F 11/00

US CL :141/31

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 141/31, 1, 130, 284; 73/864.02, 864.72; 422/100

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, search terms: capillary, bias?, spring#, decelerat?, accelerat?, impact#, shock#, impulse#, hit#, tap#, knock#, drop#

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P ----- Y, P	US 5,807,522 A (BROWN et al.) 15 September 1998, see col. 7, lines 17-30.	1-3, 11-14, 16-18, 22-24 ----- 7-9, 15, 19, 20
Y, P	US 5,770,151 A (ROACH et al.) 23 June 1998, col. 4, lines 5-6.	7
Y	US 3,358,496 A (FARMER) 19 December 1967, col. 1, lines 34-48.	8, 9
Y	US 3,568,735 A (LANCASTER) 09 March 1971, col. 2, lines 61-70.	15, 19, 20



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

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